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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/384,959	08/27/1999	RAM SASISEKHARAN	M0656/7046HC	8533

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WOLF GREENFIELD & SACKS, PC
FEDERAL RESERVE PLAZA
600 ATLANTIC AVENUE
BOSTON, MA 02210-2211

EXAMINER

HUTSON, RICHARD G

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/384,959	Applicant(s) SASISEKHARAN ET AL.	
	Examiner Richard G. Hutson	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 June 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 30-34, 46-49 and 58-60 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 30, 32-34, 46-49, 58-60 is/are rejected.
- 7) ☒ Claim(s) 31 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>6/2004</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicants amendment of claims 30, 33 and 46 and the addition of new claims 58-60, in the paper of 6/14/2004, is acknowledged and has been entered. Applicants' arguments filed on 6/14/2004, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 30-34, 46-49 and 58-60 are at issue and are present for examination.

Claim Objections

Claim 31 is objected to because of the following informalities:

Claim 31 depends from rejected claim 30.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30, 32, 33, 34, 46, 47, 48, 49 and 58-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for those methods of cleaving a heparin-like or heparan sulfate-like

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glycosaminoglycan comprising contacting said heparin-like or heparan sulfate-like glycosaminoglycan with a modified heparinase II comprising SEQ ID NO: 2 or heparinase I comprising SEQ ID NO: 4 with a substitution at a specific histidine or cysteine 348, does not reasonably provide enablement for those methods of cleaving a heparin-like or heparan sulfate-like glycosaminoglycan comprising contacting said heparin-like or heparan sulfate-like glycosaminoglycan with any modified heparinase II comprising SEQ ID NO: 2 or heparinase I comprising SEQ ID NO: 4 or having **conservative substitutions thereof**, with a substitution at a specific histidine or cysteine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 30, 32, 33, 34, 46, 47, 48, 49 and 58-60 are so broad as to encompass any method of cleaving a heparin-like or heparan sulfate-like glycosaminoglycan comprising contacting said heparin-like or heparan sulfate-like glycosaminoglycan with any modified heparinase comprising SEQ ID NO: 2 or SEQ ID NO: 4 or **conservative substitutions thereof**. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of modified heparinase II enzymes broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids

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in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the claimed methods using those modified heparinase II enzymes having the amino acid sequence of SEQ ID NO: 2 or 4 with a substitution at a specific histidine or cysteine.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all methods of using any modified heparinase, from any species, having the amino acid sequence of SEQ ID NO: 2, 4 or conservative substitutions thereof, because the specification does not establish: (A) regions of the protein structure which may be modified without effecting heparinase activity; (B) the general tolerance of heparinases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues of any heparinase with an expectation of obtaining the desired biological

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function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including methods involving any number of amino acid modifications of any heparinase. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those modified heparinase enzymes having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

This rejection was made in a previous office action, 2/25/2003, on the basis that applicants specific reference to the functional language of a specific product profile was not enabled. Applicants amended the claims and traversed the rejection as it applied to the amended claims and the rejection was withdrawn based on applicants amendment. Upon further consideration the rejection is maintained based on applicants claimed methods of use of any heparinase II or I having the amino acid sequence of SEQ ID NO: 2 or 4 and **conservative substitutions thereof**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number

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is (571) 272-0930. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink, appearing to read 'Richard G. Hutson', with a long horizontal line extending to the right.

Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rg
9/1/2004